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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/608,713	06/30/2000	Hideo Ago	SHIM-007	2056

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EXAMINER
LY, CHEYNE D

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 09/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/608,713	Applicant(s) AGO ET AL.	
	Examiner Cheyne D Ly	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-36* is/are pending in the application.

4a) Of the above claim(s) *19-29,32 and 34-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *19-36* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traversal of Group IV, claims 30-33, in Paper No. 8, filed October 3, 2001, is acknowledged.

2. The traversal is on the ground(s) that it would not be unduly burdensome to perform a search on claims 1-29 together. This is not found persuasive because nucleic acids and polypeptides are directed to different chemical types regarding the critical limitations therein. Further, the distinct methods of use corresponding to each chemical type support the undue search burden if they were examined together. While taking advantage of the distinct properties of each chemical type, these usages have distinct goals as requiring distinct and different functions and results thereof without overlapping search due to different subject matter. This lack of overlapping searches documents the undue search burden if they were search together.

3. The requirement is still deemed proper and is therefore made FINAL.

4. Claim 32 is withdrawn from examination because this dependent claim of the parent claim number 29 of Group III was inadvertently included in this Group under the Restriction Requirement dated August 28, 2001.

5. Claims 30, 31, 33 are examined on the merits.

INFORMATION DISCLOSURE

6. The information disclosure statement filed October 2, 2000 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered.

LACK OF ENABLEMENT UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 30, 31, and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an HCV polymerase which have atom coordinates instantly disclosed, does not reasonably provide enablement for an HCV polymerase inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

8. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

9. It is acknowledged that the applicant has disclosed information to enable one skilled in the art to make a crystal of the HCV polymerase using SEQ ID NO:2 of $NS5B_{570}$ (Examples 1-3, Pages 20-277). However, claims 30, 31, and 33 are drawn to methods of designing or identifying HCV polymerase inhibitors based on the data generated from the HCV polymerase crystal structure. It is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). In light of the difficulty of the protein crystallization process, it is, therefore, unreasonable to expect one skilled in the art to use the information disclosed for one specific crystal to make other of predictable quality that are different from the crystal disclosed in the specification without undue experimentation. Specific to the HCV polymerase, it is unlikely for one skilled in the art to use the information disclosed for one specific crystal to make others of predictable quality where the C-terminal amino acid of residue X is any one of amino acid residues 531(Lys) to 570 (Arg) of the NS5B. Furthermore, the unreliability of the protein crystallization process makes it even more unlikely for one skilled in the art to use the information disclosed for one specific crystal to reliably predict the three-dimensional structure of a test compound without actually generating a crystal structure of the said test compound.

10. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for identification of inhibitors for the HCV polymerase via reacting a template RNA and substrates in the presence of a test compound, does not reasonably provide enablement for determining HCV polymerase activity via reacting a template RNA and substrates in the absence of a test compound and comparing the HCV polymerase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to use the invention commensurate in scope with these claims. It is acknowledged that the applicant has disclosed information to enable one skilled in the art to determine activity of HCV polymerase in the presence of a test compound (Example 7, pages 280- 282). However, claim 33 is drawn to a method of identifying HCV polymerase inhibitors via comparing HCV polymerase activity in the presence of a test compound to HCV polymerase activity in the absence of a test compound. The critical limitation within this claim is that the HCV polymerase activity is determined by the difference of enzymatic activity in the presence and absence of a test compound. The lack of disclosure of how one would determine the HCV polymerase activity in the absence of a test compound, then, compare the said activity to the activity in the presence of a test compound does not enable one skilled in the art to use this method to identify HCV polymerase inhibitors. Therefore, this lack of disclosure by the Applicant provides sufficient support that claim 33 does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope of this claim.

INDEFINITENESS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 30, 31 and 33 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. In the case of claims 30 and 31, the preamble limitations comprise of a method for designing or identifying HCV polymerase inhibitors. As disclosed in the specification (Page 18,

lines 9-36 and page 19, lines 1-18), the design process begins with analyzing the HCV polymerase inhibitors of the active site. The three-dimensional structural information is obtained and a hypothetical compound having the structural complementarity with the active site that is verified by using computers, and a leading compound having the complementarity with the active site can be designed. While the HCV polymerase inhibitors identification process (Example 7, pages 280-282) begins with the three-dimensional structural analysis of $NS5B_{570}$. A comparison of the said three-dimensional structural information to that of other variants is made to confirm the RNA binding cleft as target for the polymerase inhibitors. The measurements of HCV polymerase activity of different variants are used to isolate polypeptide regions where compounds of similar structure could be generated as polymerase inhibitors. A computational analysis is used to confirm the inhibitor and active site interactions. Then, the select compounds are synthesized. It can be inferred from the specification that these distinct methods for designing and identifying HCV polymerase inhibitors rely on the data from the three-dimensional structural information generated from the HCV polymerase crystal. However, they differ with respect to their starting points and goals. Design starts with using three-dimensional structural information to derive a hypothetical test compound and this compound is later made and verified via enzymatic activity. While, the identification process starts with an identified list of existing variant polymerases and some these variants are selected based their enzymatic activities. This process concludes with the identified polypeptides being synthesized. The inclusion of these two distinct methods within the preamble of each claim supports that claims 30 and 31 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claims 30, 31, and 33 are regarded as indefinite because the Applicant fails to support each method of the preamble with their respective active steps. The active steps of the claims exhaustively describe the steps necessary for evaluating the HCV polymerase NS5B. However, the active steps of each claim do not help the Applicant accomplish the intended goal of each method, designing or identifying, in the preamble of the said claims. Nor do the active steps clearly and definitively establish support for each distinct method, designing or identifying, within the preamble. A question that comes to mind is which component, the preamble or the active steps, of the claims is controlling these claims. Currently, it is inconclusive as to which component is controlling the claims or how one is to design or identify polymerase inhibitors according to these methods.

15. No claim is allowed.

CONCLUSION

16. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 193), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (703) 308-3880. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

18. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

19. Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
9/24/02